Int. J. Cancer: **113,** 1002–1004 (2005)

Birth size and subsequent risk for prostate cancer: A prospective population-based study in Norway

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Studies on birth size characteristics and adult risk for prostate cancer have been few and inconclusive. We prospectively examined the association between birth size and risk for prostate cancer with particular emphasis on metastatic disease. A total of 19,681 singleton males born between 1920 and 1958, whose birth records were kept at St. Olav's University Hospital (Trondheim, Norway), were followed up for prostate cancer by linkage to the Norwegian Cancer Registry. A total of 159 cases of prostate cancer were diagnosed during follow-up; 33 had metastases at diagnosis. Overall, there was little evidence for any association between birth size and prostate cancer risk; however, there was a positive association for birth size and metastatic disease. Men in the highest quartile of birth length (≥53 cm) had a relative risk of 2.5 (95% CI 1.0–6.3) compared to men in the lowest quartile (<51 cm). Further, men in the highest quartile of both birth weight and birth length had a relative risk of 3.8 (95% CI 1.2–12.0) for metastatic prostate cancer compared to men in the lowest category of both factors. These results support the hypothesis that factors that determine intrauterine growth could be important for aggressive forms of prostate cancer in adulthood.

Key words: prostate cancer; metastasis; birth weight; birth length; head circumference

Few epidemiologic risk factors have been identified for prostate cancer, although its etiology is hypothesized to be hormonal. Recent interest in the influence of the intrauterine period is partly a response to studies that have shown associations between early life factors and breast cancer, another hormone-related malignancy. A positive association between birth size and breast cancer risk has been reported in many studies,[1–5] but only a few studies have assessed birth size in relation to prostate cancer risk.[6–10] The earliest study found a strong positive association with birth weight,[6] but subsequent studies failed to confirm an overall positive association.[7–10] In one of these studies, however, there was a modest positive association between birth weight and risk for aggressive prostate cancer, as indicated by advanced stage at diagnosis;[8] and another study reported a positive association between birth weight and prostate cancer mortality.[7]

In nearly 20,000 Norwegian men born between 1920 and 1958, we studied prospectively the risk for prostate cancer related to birth weight, birth length and head circumference. In particular, we emphasized the risk for advanced disease, indicated by the presence of metastases at diagnosis.

Material and methods

Material

We abstracted information on birth size from records of all births that occurred at St. Olav's University Hospital (Trondheim, Norway) from 1920 to 1958, including 22,270 male offspring.

In 1960, every Norwegian citizen was assigned a unique 11-digit identification number, and each citizen's record is continuously updated on vital status and residential history through the national Central Person Registry. Using a person's name and date of birth combined with the mother's name, we identified men who were born at St. Olav's Hospital between 1920 and 1958 who were alive in 1960. For some men whose mothers died before 1960, identity could not be confirmed. Thus, among a total of 21,703 male singleton births, we reliably identified 19,681 (91%) men for whom linkage with the Norwegian Cancer Registry to ascertain prostate cancer was possible. For men who were 20 years or older in 1960 (born 1920–1940), follow-up for prostate cancer started January 1, 1961. Men born after 1940 were followed up from their 20th birthday. Follow-up ended when a cancer (at any site) was diagnosed, at emigration, at death or on December 31, 2001, whichever occurred first.

The reporting of cancer to the Norwegian Cancer Registry is mandatory, and prostate cancer was registered according to the ICD-7 (code 177). During 41 years of follow-up (median 31.4 years), 159 men were registered as new cases of prostate cancer, and 33 of them presented with metastases. Registration of metastatic disease in the Norwegian Cancer Registry is based on compulsory reported information from pathology and clinical departments. Validation of this information related to prostate cancer has been reported and judged to be very satisfactory.[11]

Median age at diagnosis of prostate cancer was 65 years (range 41–81), reflecting the relatively young distribution of the cohort. During follow-up, 1,110 men were censored when they were diagnosed with other cancers, 1,621 when they died from causes other than cancer and 451 when they emigrated and could no longer be traced.

Information on birth weight (g), birth length (cm), head circumference (cm), length of gestation (weeks or months) and birth order was abstracted from birth records. We also abstracted information on maternal age, height and socioeconomic status (according to the father's or the mother's own occupation) at birth.

Statistical methods

We categorized the birth size variables (birth weight, birth length and head circumference) into 4 approximately equal categories (approximate quartiles). We used Cox regression analysis to estimate relative risks (RRs) for prostate cancer associated with each of the birth size characteristics. Precision of effects was estimated using 95% confidence intervals (CIs), and p values for trend tests were calculated by treating the birth size categories as ordinal variables in the regression model. To adjust for cohort effects, we included birth year in 5-year intervals (1920–1958). Multivariable analyses were conducted to assess potential confounding by maternal age (5-year categories) at childbearing, length of gestation, birth order (1, 2, 3, ≥4), maternal height and indicators of socioeconomic status. Length of gestation was categorized as preterm (before 37 weeks or in the seventh or eight month), term (at week 37–41 or in the ninth month) or postterm (after 41 weeks or in the tenth month). As indicators of socioeconomic status, we used the

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Received 2 June 2004; Accepted after revision 12 August 2004
DOI 10.1002/ijc.20674
Published online 28 October 2004 in Wiley InterScience (www.interscience.wiley.com).

woman's or her partner's occupation at the time of childbearing.

Initially, we assessed the associations of birth size indicators with overall risk for prostate cancer and, in subsequent analyses, the associations with prostate cancer that presented with metastases.

Results

Positive but weak associations were found between overall risk for prostate cancer and both birth weight and birth length (Table I). Men in the highest quartile of birth weight (≥3,925 g) had an RR of 1.3 (95% CI 0.8–2.0) compared to men in the lowest category (<3,260 g), but there was no clear trend in risk across the distribution of birth weight (p for trend = 0.29). For birth length, the RR for men in the highest (≥53 cm) compared to the lowest (<51 cm) category was 1.2 (95% CI 0.7–2.0). In relation to head circumference, there was no clear association with risk of prostate cancer. Adjustment for potential confounding by maternal age at childbearing, length of gestation, birth order, maternal height and socioeconomic status did not substantially alter these results. Overall risk for prostate cancer was not related to maternal age or birth order (data not shown).

In subsequent analysis of the 33 men who presented with metastatic prostate cancer, associations with birth size were stronger than for overall prostate cancer risk (Table II). Comparing men in the highest (≥3,925 g) with men in the lowest (<3,260 g) quartile of birth weight, those who were heavier at birth had an RR of 1.5 (95% CI 0.6–3.7). For birth length, men in the highest (≥53 cm) category had an RR of 2.5 (95% CI 1.0–6.3) compared to men in the lowest (<51 cm) category. Further, we compared men who belonged to the highest category of both birth weight and birth length with men who were in the lowest category of both factors. We found that risk for metastatic prostate cancer was nearly 4 times higher (RR = 3.8, 95% CI 1.2–12.0) in the larger group. Adjustment for the potentially confounding factors mentioned above did not substantially influence these results.

TABLE I – RR FOR PROSTATE CANCER ASSOCIATED WITH BIRTH SIZE CHARACTERISTICS

	Number of cases[1]	Number of men[1]	RR (95% CI)[2]	p_{trend}[3]
Birth weight (g)				
<3,260	38	4,969	1.0	
3,260–3,590	39	4,829	1.2 (0.8–1.9)	
3,595–3,920	39	5,017	1.1 (0.7–1.8)	
≥3,925	43	4,861	1.3 (0.8–2.0)	0.29
Birth length (cm)				
<51	79	6,724	1.0	
51	27	3,715	0.9 (0.6–1.4)	
52	35	4,028	1.6 (1.1–2.4)	
≥53	18	5,205	1.2 (0.7–2.0)	0.16
Head circumference (cm)				
<35	42	4,782	1.0	
35	36	5,092	0.8 (0.5–1.3)	
36	39	5,124	0.9 (0.6–1.3)	
≥37	42	4,612	1.1 (0.7–1.8)	0.54

[1]Information on every variable was not available for all participants.–[2]Adjusted for year of birth (1920–1924, 1925–1929· · ·1955–1958).–[3]Two-sided p values for trend in Cox regression.

TABLE II – RR FOR METASTATIC PROSTATE CANCER ASSOCIATED WITH BIRTH WEIGHT AND BIRTH LENGTH

	Number of cases[1]	Number of men[1]	RR (95% CI)[2]	p_{trend}[3]
Birth weight (g)				
<3,260	8	4,969	1.0	
3,260–3,590	7	4,829	1.0 (0.4–2.8)	
3,595–3,920	8	5,017	1.1 (0.4–3.0)	
≥3,925	10	4,861	1.5 (0.6–3.7)	0.41
Birth length (cm)				
<51	18	6,724	1.0	
51	6	3,715	0.9 (0.4–2.3)	
52	2	4,028	0.5 (0.1–2.1)	
≥53	7	5,205	2.5 (1.0–6.3)	0.30

[1]Information on every variable was not available for all participants.–[2]Adjusted for year of birth (1920–1924, 1925–1929· · ·1955–1958).–[3]Two-sided p values for trend in Cox regression.

Discussion

In our large prospective study of Norwegian men, we found a relatively strong positive association between birth size and risk for metastatic prostate cancer. In relation to prostate cancer overall, however, we observed only weak positive associations with birth size characteristics (weight and length).

Previously, a small Swedish cohort study found that men in the highest category of birth weight were at higher overall risk for prostate cancer than other men,[6] but subsequent studies could not confirm this association.[7,9] In one of these studies, however, a positive association between birth weight and prostate cancer mortality was reported.[7] Two studies from the United States also reported no overall association between birth weight and prostate cancer risk;[8,10] but in one of them, there was a weak positive association between birth weight and aggressive disease, as indicated by advanced stage at diagnosis.[8]

In relation to birth length, the Swedish studies mentioned above found no association with overall risk for prostate cancer.[7,9] One case-control study, however, reported a modestly higher likelihood for prostate cancer among men who were in the highest category of birth length.[10]

In our study, the positive association with birth length was restricted to aggressive prostate cancer, as indicated by the presence of metastases at diagnosis. This information is based on a combination of pathology and clinical reports, both of which are compulsory for the Norwegian Cancer Registry. Moreover, the quality of the prostate cancer data has been examined and found to be very satisfactory.[11] Combined with the evidence from other studies, our finding suggests that there is a positive association between birth size and risk for prostate cancer with life-threatening potential but no association with less aggressive disease.

The prospective design of our study makes it unlikely that bias can explain the results. Another strength of our study is the availability of perinatal information from birth records with measured, as opposed to self-reported, values of birth length and birth weight. Also, the complete follow-up for prostate cancer incidence of a large and unselected population strengthens the validity of our findings. The lack of information on other potential confounding factors in adulthood could be viewed as a weakness; however, there are few, if any, established adult risk factors for prostate cancer.

Previously, it was suggested that the intrauterine environment could be important for prostate cancer development, implicating pregnancy hormones, *e.g.,* estrogens, testosterone and IGFs.[12–14] It is essential to identify the relevant hormonal mechanisms that influence intrauterine growth, their external determinants and how their activity may be modulated by other factors, including the role of prenatal and postnatal nutrition.[13] Other determinants of birth size may also be important, and our results suggest that determinants of intrauterine longitudinal growth may be particularly relevant.

In conclusion, our results suggest that intrauterine factors may influence the risk for prostate cancer in adulthood, but the effect appears to be confined to prostate cancer with life-threatening potential.

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